swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Anzupgo

International non-proprietary name:	delgocitinib
Pharmaceutical form:	cream
Dosage strength(s):	20 mg/g
Route(s) of administration:	cutaneous use
Marketing authorisation holder:	Leo Pharmaceutical Products Sarath Ltd.
Marketing authorisation no.:	69330
Decision and decision date:	approved on 13 November 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the plasma concentration-time curve
BAV	Bioavailability
CHE	Chronic hand eczema
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
EMA	European Medicines Agency
ERA	Environmental risk assessment
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IGA	Investigator's global assessment
IL	Interleukin
INN	International non-proprietary name
JAK1/2/3	Janus kinase 1/2/3
LoQ	List of Questions
LTE	Long-term extension
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
NO(A)EL	No observed (adverse) effect level
PIP	Paediatric investigation plan (EMA)
PUVA	Psoralen plus ultraviolet A
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TYK2	Tyrosine kinase 2
UGT	Uridine diphosphate-glucuronosyltransferase

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for delgocitinib in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to topical corticosteroids, or for whom topical corticosteroids are not advisable.

2.2.2 Approved indication

Anzupgo® is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom a treatment with potent to very potent topical corticosteroids is not recommended. Avoiding contact with the triggering noxa, skin protection and basic care are important components of the therapy.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Twice daily application to the affected skin of the hands and wrists until the skin is clear or almost clear.
In the event of recurrence of the signs and symptoms of CHE (flares), twice daily treatment of the affected areas should be re-initiated as needed.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	8 August 2023
Formal control completed	16 August 2023
List of Questions (LoQ)	24 November 2023
Response to LoQ	24 March 2024
Preliminary decision	21 July 2024
Response to preliminary decision	20 August 2024
Response to labelling corrections and/or other aspects	25 October 2024
Final decision	13 November 2024
Decision	approval

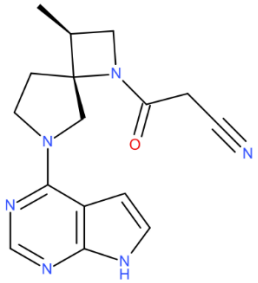
3 Medical context

Chronic hand eczema (CHE), or hand dermatitis, is a common, inflammatory disorder involving the skin of the hands and persisting for more than 3 months, or recurring 2 or more times within a 12-month time frame.
Typical clinical signs include redness, thickening of the skin, scaling, oedema, vesicles, areas of hyperkeratosis, cracks (fissures), and erosions. Symptoms may include itching, burning, or stinging. Severe hand eczema can affect the patient's psychosocial functioning and general well-being.
The pathogenesis of hand eczema is multifactorial and involves both genetic and environmental factors (e.g., wet work, irritants/allergens). Hand eczema is the most frequent occupational skin disease, especially among workers exposed to "wet work," such as healthcare workers, food handlers, and hairdressers. Hand eczema may also be a manifestation of a number of eczemas, most frequently atopic hand eczema and irritant contact dermatitis.

Currently available treatment options for moderate to severe chronic hand eczema are topical corticosteroids (typically potent to high-potent), psoralen plus ultraviolet A (PUVA) or UV-B therapy and, for severe cases only, oral alitretinoin. Oral corticosteroids are worst-case treatment options. Even though topical corticosteroids are effective, long-term treatment is associated with increased side effects and to be avoided. In Switzerland, alitretinoin is approved for the treatment of severe CHE only, and associated with severe risks such as teratogenicity. So, there remains an unmet medical need for corticosteroid-free, topical treatments for CHE.

4 Quality aspects

4.1 Drug substance

INN:	delgocitinib
Chemical name:	3-[(3S,4R)-3-Methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl]-3-oxopropanenitrile
Molecular formula:	$C_{16}H_{18}N_6O$
Molecular mass:	310.35 g/mol
Molecular structure:	

Physicochemical properties: Delgocitinib is a white to almost white powder. Delgocitinib is freely soluble in an aqueous solution at pH 3.

Synthesis: The drug substance is manufactured by a multiple step chemical synthesis with final crystallisation. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specification: The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure a consistent quality of delgocitinib.

Stability: Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug product

Description and composition: The drug product is a white to slightly brown cream in which the drug substance (20 mg/g) is completely dissolved in the aqueous phase.

Pharmaceutical development: Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.

Manufacture: The manufacturing of the drug product is a standard process used for semi-solid manufacturing which includes the preparation of the aqueous phase, preparation of the fat phase, and emulsification.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include the parameters appearance (visual examination), identity (HPLC, UV), assay (HPLC), degradation products (HPLC), pH, viscosity, and microbial tests. Analytical methods have been described and validated according to ICH requirements.

Container closure system: Delgocitinib drug product is packaged in laminate tubes with cap.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Delgocitinib is an ATP-competitive inhibitor of human Janus kinase 1 (JAK1), JAK2, JAK3, and tyrosine kinase 2 (TYK2) with K_i values of 2.08, 1.71, 5.45, and 13.9 1nM, respectively. It inhibited phosphorylation of signal transducers and activators of transcription (STAT) induced by interleukin (IL)-2, IL-6, IL-23, interferon (IFN)-α, and granulocyte macrophage-colony stimulating factor (GM-CSF) with IC_{50} values of 39.6, 32.5, 84.3, 18.1, and 304 nM, respectively. Delgocitinib suppressed IL-2-induced cell proliferation of human, rat, and mouse T cells with IC_{50} values of 8.9, 15.3, and 10.9 nM, respectively. Furthermore, it inhibited IL-21-mediated proliferation of human B cells (in the presence of CD40), IL-13 secretion by human mast cells (stimulated with IL-4 and IgE-crosslinking), and tumour necrosis factor alpha (TNF-α) production by activated human monocytes (induced by GM-CSF in the presence of lipopolysaccharides) with IC_{50} values of 49.2, 135, and 277 nM, respectively. In the absence of cytokines, delgocitinib showed no, or only little, inhibitory effect on the proliferation of human lung fibroblasts at concentrations of up to 10 µM. Finally, it reversed IL-4 and IL-13-mediated reduced mRNA expression of skin barrier-related proteins in primary human epidermal keratinocytes.

In mice with 2, 4-dinitrofluorobenzene-induced dermatitis, oral administration of delgocitinib at ≥3 mg/kg/day suppressed skin inflammation. Topical administration of delgocitinib as ≥0.3% ointment suppressed skin inflammation in a similar rat model of dermatitis. Repeated topical application as a 3% ointment did not affect skin thickness in healthy rats. Topical delgocitinib also improved skin barrier function *in vivo* in a dry skin mouse model. Finally, both oral and topical delgocitinib suppressed IL-31-induced scratching behaviour in mice.

In conclusion, the pharmacology of delgocitinib as a pan-JAK inhibitor for the treatment of dermatitis has been sufficiently characterised from a nonclinical perspective.

Delgocitinib inhibited Rho-associated protein kinase 2 (ROCK2) with an IC_{50} value of 0.141 µM (88-fold human C_{max}). No further off-target pharmacology was observed.

Safety pharmacology studies revealed a transient decrease in blood pressure and an increase in heart rate in rats and dogs at exposures exceeding 1600- and 1100-fold human C_{max}. The decrease in blood pressure results from a vasorelaxant effect of delgocitinib (likely attributed to the inhibition of ROCK2) and leads to reflex tachycardia. There were no effects on the central nervous system in rats (at up to 4100-fold human C_{max}) or the respiratory system in dogs (at up to 3300-fold human C_{max}). In rats, delgocitinib decreased gastro-intestinal charcoal transport and increased urinary K^+ excretion at exposures above 1600-fold human C_{max}.

5.2 Pharmacokinetics

After topical (dermal) application, bioavailability (BAV) of delgocitinib in rats was 2.6% for intact skin and 5.4% for damaged skin. In minipigs, BAV was ≤0.88% for the cream and ≤1.57% for the ointment. BAV was similarly low in humans (0.6% for the cream). After dermal application of delgocitinib ointment to minipigs, both C_{max} and AUC increased with the dose. Systemic exposure increased after repeated dosing with no clear differences from Week 13 onwards. There were no clear sex-related differences in exposure.

Plasma protein binding of delgocitinib was similarly low (18%-29%) in mice, rats, rabbits, dogs, minipigs, and humans. Distribution into blood cells was similar in rats, dogs, and humans (55%-60%). After dermal application, delgocitinib-related radioactivity was mainly observed in the skin at the application site. Delgocitinib and/or its metabolites showed affinity for melanin. Delgocitinib-derived

radioactivity crossed the rat placenta but was very low in whole fetuses (≤0.03% of total radioactive dose).

Delgocitinib was metabolised by CYP1A1, CYP2C19, CYP2D6, and CYP3A4. Postulated metabolic pathways of delgocitinib include oxidation of the side chain of the azetidine ring to M1, oxidation of the pyrrolo-pyrimidine ring to M2 or M3, oxidation of the spiro ring to M4, and glucuronide conjugation to M5. The major component in rat, dog, and human plasma was delgocitinib. M1, M3, M4, and M5 were only minor metabolites in human plasma and all of them were detected in animals (after oral administration).

Delgocitinib and its metabolites are excreted mainly via the urine and, to a lesser extent, via the faeces, mostly as unchanged delgocitinib (and M3 in dogs). Delgocitinib-related radioactivity was detected in rat milk, with an AUC almost 3-fold plasma AUC. In the absence of human data, delgocitinib should not be used during lactation.

5.3 Toxicology

The applicant conducted a full toxicology programme in line with ICH M3(R2). The repeat-dose toxicity studies were conducted in rats, dogs, and minipigs. These species are considered pharmacologically relevant. Delgocitinib was administered orally in the rat and dog studies, which resulted in high systemic exposures and is, therefore, suitable for characterising the toxicity of delgocitinib. In minipigs, the adequate species for the assessment of topical formulations, delgocitinib was administered topically, in line with the intended clinical route of administration. The duration of the repeat-dose toxicity studies (up to 6 months in rats and 9 months in dogs and minipigs) is appropriate for a product intended for long-term/intermittent use.

Single oral doses of delgocitinib resulted in mortality at 1000 mg/kg (69,000-fold human C_{max}) in mice and at 300 mg/kg (approximately 41,000-fold human C_{max}) in rats. In the repeat-dose toxicity studies, systemic toxicity was only noted after oral administration in rats and dogs. Main findings included decreases in white blood cells and associated atrophic changes in lymphoid organs, and red blood cell parameters. These changes were reversible and considered an effect of JAK inhibition. In the 9-month dog study, the immunosuppressive effect ultimately resulted in opportunistic infections in dogs (in particular demodicosis) that were identified from Week 16 onwards at 3 mg/kg/day (exposure 1100-fold human AUC at clinical dose) and resulted in premature terminations. The immunosuppressive effect of delgocitinib was also evidenced by impaired T-cell dependent B-cell (antibody) response and decreased lymphocyte subsets in peripheral blood and thymus. The observed transient reddening of skin in mice and rats, and auricles and visible mucous membranes in dogs after dosing were considered to result from the vasorelaxant effect of delgocitinib (see “Safety pharmacology” section). Safety margins based on AUC at the NOAEL in the pivotal/chronic repeat-dose toxicity studies with oral administration were high (161- to 508-fold). No systemic or dermal toxicity was observed in minipigs with topical delgocitinib (ointment) at the maximum feasible dose resulting in systemic exposures up to 11- to 20-fold human AUC.

Delgocitinib was not genotoxic. Topical delgocitinib was not carcinogenic in mice. The Leydig cell tumours and pancreatic acinar cell adenomas observed in rats were considered to be rat-specific, whereas both thymoma and lipoma formation were likely a result of JAK inhibition. However, as delgocitinib did not induce tumours in mice after topical administration and since high (650-fold) safety margins were achieved, the applicant concluded that there was no appreciable carcinogenic risk for humans at therapeutic topical exposure. Nevertheless, the findings in rats are mentioned in the Information for healthcare professionals.

Delgocitinib did not impair fertility in male rats at exposures up to 1700-fold human AUC. Both fertility and early embryonic development were affected in female rats, but only at exposures exceeding

1100-fold human AUC for female fertility and 110-fold human AUC for early embryonic development. Delgocitinib showed embryofetal lethality and fetal growth retardation in rats and rabbits. Some skeletal variations were also observed in rats. However, at the NOAEL for embryofetal toxicity, exposure was 120-fold human AUC in rats and 195-fold human AUC in rabbits. In the pre- and postnatal development study in rats, delgocitinib prolonged gestation length and parturition, and decreased viability of fetuses. In the offspring, there was a decrease in viability and body weight, although physical development, behaviour, learning and memory, sexual maturation, and reproductive performance were not affected. Exposure at the NOAEL for both F0 dams and F1 offspring was 510-fold human AUC. In conclusion, animal studies showed reproductive toxicity but safety margins were >100-fold based on AUC. Nevertheless, in the absence of human data, as a precautionary measure, it is preferable to avoid the use of delgocitinib during pregnancy. The toxicity study in juvenile rats with oral administration of delgocitinib starting from postnatal day 21 did not reveal any additional target organ. Exposure at the NOAEL was 1300-fold (males) and 1700-fold (females) human AUC.

Local tolerance of the 2% cream (formulation almost identical to that intended to be marketed) was confirmed in minipigs. Delgocitinib ointment (up to 3%) was not irritant to the eye *in vitro*, did not show any skin sensitisation, photosensitisation, or phototoxic potential in guinea pigs. No phototoxic potential was observed in mice after oral administration either. Local tolerance as well as photosensitisation and phototoxic potential of delgocitinib cream 2% were assessed clinically.

There were no issues with impurities.

The applicant provided a satisfactory ERA. All relevant nonclinical safety findings are included in the nonclinical part of the safety specification of the RMP. The toxicity studies requested in the PIP were completed, and the reports are included in the marketing authorisation application.

5.4 Nonclinical conclusions

The submitted nonclinical documentation is considered adequate to support the approval of delgocitinib in the proposed indication. All safety-relevant nonclinical data are included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption
The absorption and systemic exposure of delgocitinib was assessed by comparing plasma concentrations after oral application and after topical administration. The mean systemic exposure after topical administration does not show accumulation and, on average, a relative bioavailability of 0.6% was found. A high variability in the systemic exposure was observed, and the variability was driven to a similar extent by inter-occasional (between applications) and inter-subject (between patients) variability. Therefore, it cannot be excluded that pharmacologically relevant systemic exposures are reached temporarily. After multiple cream applications, a flat exposure curve was observed, indicating a flip-flop kinetic where the observed clearance of the delgocitinib is driven by the slow absorption from the skin.

Distribution
Based on an *in vitro* study, delgocitinib plasma protein binding is low, with a range of 22% to 29%. The apparent volume of distribution after single oral doses in healthy volunteers was in the range of 100 to 200 L. The volume of distribution was not assessed after topical application in patients.

Metabolism
Based on *in vitro* assays in liver microsomes and cytochrome P450 inhibitors, delgocitinib was mainly metabolised by CYP3A4/5, with minor contributions from CYP1A1, 2C9, 2C19, and 2D6. The highest abundance was found for metabolite M5, which is formed through glucuronidation. The enzymatic specificity for UGTs was not assessed.

Elimination
The elimination rate was assessed after oral and topical administration. After oral administration, an elimination half-life of 2 to 4 hours has been found, and after topical application a half-life of 20.3 h was estimated. The major elimination pathway is unchanged in urine after oral application.

Intrinsic and extrinsic factors

No trends in systemic exposures were observed based on gender, body weight, or race.

The amount of delgocitinib cream used by the patients is an extrinsic factor influencing the observed systemic exposure of delgocitinib. For the average application above 20 mg of delgocitinib, limited data are available. 20 mg delgocitinib per application corresponds approximately to 60 g cream usage per month with 1 g cream usage per application.

Other factors identified to show a tendency to higher plasma exposure could be attributed either to reduced skin integrity (geriatric patients, higher fissure score), or reduced clearance (renal impairment).

Interactions

Effect of other drugs on delgocitinib
The major route of elimination is unchanged delgocitinib in urine. Therefore, there is a low risk of other drugs affecting the exposure of delgocitinib.

Effect on other drugs
Enzymatic inhibition and induction potential was assessed *in vitro*, and no interaction potential was found at relevant concentrations.

Safety pharmacology

QT prolongation
A clinical trial to evaluate QTcF prolongation and the proarrhythmic potential of delgocitinib following oral administration in healthy subjects was conducted. The systemic concentrations achieved in the TQT study were multiple times above the individual peak plasma concentrations observed after dermal application of delgocitinib cream in CHE trials, and no risk of QT prolongation was identified.

Phototoxic and photoallergic potential
Dedicated clinical trials to evaluate the phototoxic and photoallergic potential of delgocitinib cream after topical application on healthy skin were conducted. Dosage strengths of the market formulation (20 mg/g) were investigated, and no risks for phototoxic or photoallergic potential were identified.

6.2 Dose finding and dose recommendation

One Phase 2b, double-blind, multi-centre, randomised, parallel-group, vehicle-controlled, dose-finding study (study 1273) was submitted in order to establish dose-response and to investigate the efficacy and safety of a twice-daily topical application of delgocitinib cream in adult patients with mild to severe chronic hand eczema (CHE).

Patients could be included if they were 18 years or older. They had to have a diagnosis of CHE, defined as a hand eczema that had persisted for more than 3 months or had returned at least twice within the last 12 months. The CHE had to be of mild to severe grade according to the Investigator's Global Assessment for CHE (IGA-CHE, henceforth "IGA"), with a score of 2 defined as mild, 3 as moderate, and 4 as severe CHE. Furthermore, the patients had to have a recent history (within 1 year before screening) of inadequate response to topical corticosteroids or of topical corticosteroids being medically inadvisable. Diagnostic patch testing had to have been performed within 3 years prior to screening.

The screening period had a duration of between 1 and 4 weeks.
Eligible patients were randomised 1:1:1:1:1 to 1 of 5 treatment groups for 16-week treatment with either delgocitinib cream 1, 3, 8, or 20 mg/g, or vehicle cream. The randomisation was stratified by the severity of CHE according to the IGA score 2, 3, or 4.
During the treatment period, the respective study product was applied topically twice daily on the hands for 16 weeks.
If medically necessary, rescue treatment for CHE was allowed, but those patients were considered as non-responders.
Individual study participation ended with a follow-up visit approx. 2 weeks after the last application (Week 18).

The primary endpoint was defined as the proportion of patients achieving an IGA score of 0 (clear) or 1 (almost clear), with an at least 2-step improvement from baseline. The difference in response rates between each of the active delgocitinib doses and vehicle was analysed separately using the Cochran-Mantel-Haenszel test.
Compared to the vehicle, a statistically significant and clinically relevant treatment effect of delgocitinib 8 mg/g and 20 mg/g was demonstrated ($p = 0.0004$, each), with 20 mg/g showing the biggest difference to the vehicle cream (37.8% vs 8.0%, respectively).

Results including only patients with moderate or severe CHE were consistent, as were the sensitivity analyses.

Across treatment groups, the highest proportion of responders was found in patients with moderate CHE (40/114, 35.1%) and severe CHE (11/43, 25.6%) compared to mild CHE (7/48, 14.6%). Patients with moderate CHE had the highest response on 8 mg/g (58.3%; 20 mg/g 41.4%), patients with severe CHE on 20 mg/g (50.0%; 8 mg/g 30.0%).

The safety evaluation revealed no clear dose-dependency in regard to adverse events (AEs); however, the patients in the vehicle group reported the fewest adverse events.

The applicant selected the 20 mg/g delgocitinib dose for further testing in the confirmatory Phase 3 studies. Looking at the overall study results this can be understood, as overall the 20 mg/g delgocitinib dose was the most effective dose and there was no dose-dependency of AEs. However, it would have been worthwhile to also consider the 8 mg/g delgocitinib dose for further testing in confirmatory Phase 3 studies as this dose showed almost the same efficacy as the 20 mg/g dose and may have been sufficient for patients with only moderate CHE.

6.3 Efficacy

Two identical pivotal vehicle-controlled Phase 3 studies were submitted: studies 1401 and 1402 (DELTA 1 and 2), as well as their common uncontrolled long-term extension (LTE) study: study 1403 (DELTA 3). In addition, an active controlled Phase 3 study was submitted: study 1528 (DELTA Force).

Pivotal studies 1401 and 1402 (DELTA 1 and 2)

The 2 identical pivotal studies 1401 and 1402 (DELTA 1 and 2) were Phase 3, multi-centre, randomised, double-blind, vehicle-controlled, parallel group studies in adult patients with moderate to severe CHE.

Patients could be included if they were 18 years or older. They had to have a diagnosis of CHE, defined as hand eczema that had persisted for more than 3 months or returned at least twice within the last 12 months. The CHE had to be of moderate to severe grade according to the Investigator's Global Assessment for CHE (IGA-CHE), with a score of 3 defined as moderate and 4 defined as severe CHE. The Hand Eczema Symptom Diary (HESD) itch score had to be of ≥4 points at baseline (weekly average based on the 7 days immediately preceding baseline). See Appendix (Swiss Information for healthcare professionals) for all score definitions. Furthermore, patients had to have a documented history of inadequate response to topical corticosteroids (TCS) within 1 year prior to screening, or it had to be considered medically inadvisable to treat the patients with TCS (e.g. due to major side effects or safety risks).
Patients were excluded if they had active dermatological conditions that could interfere with the assessment of CHE, such as AD requiring medical treatment on regions other than the hands and feet, active psoriasis on any part of the body, hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body, or clinically significant infections on the hands. Patients were also not eligible for the CHE studies if they had any condition which could have compromised their safety, such as clinically significant (systemic) infections, a primary immunodeficiency disorder, a history of cancer (with some exceptions), a hypersensitivity to any component(s) of the study drug, unstable internal conditions, or abnormal laboratory findings.

Studies 1401 and 1402 (DELTA 1 and 2) had a 1- to 4-week long screening period.
Eligible patients were then randomised 2:1 to 1 of 2 treatment groups for 16-week treatment with either delgocitinib cream 20 mg/g or vehicle cream and stratified by baseline IGA and region. During the treatment period, the respective study product was applied topically twice daily on the hands for

16 weeks. Rescue treatment (mostly TCS) was initiated in case of intolerable CHE symptoms (at the investigator's discretion); however, those patients were considered as non-responders.
After the 16-week treatment period, the patients either transferred to the LTE study (DELTA 3) (see below) or ended study participation after a subsequent 2-week follow-up period.
The baseline demographic and disease characteristics can be found in the Swiss Information for healthcare professionals.

The primary endpoint was defined as the proportion of patients achieving an IGA-CHE score of 0 (clear) or 1 (almost clear) at Week 16.

In both studies 1401 and 1402 (DELTA 1 and 2), a statistically significant higher number of patients achieved the primary and all secondary efficacy endpoints in the delgocitinib treatment group compared to the vehicle cream group.
In study 1401 (DELTA 1), 19.7% of the patients in the verum versus 9.9% in the vehicle arm achieved the primary endpoint. In study 1402 (DELTA 2), 29.1% of the patients in the verum versus 6.9% in the vehicle arm achieved the primary endpoint.
The pooled data of studies 1401 and 1402 (DELTA 1 and 2) show that 24.3% of the patients in the verum versus 8.4% in the vehicle arm achieved the primary endpoint.
The detailed results for the most relevant multiplicity-controlled secondary efficacy endpoints can be found in the Appendix (Swiss Information for healthcare professionals).

LTE study 1403 (DELTA 3)

The common long-term extension (LTE) of the 2 identical pivotal parent studies 1401 and 1402 (DELTA 1 and 2), study 1403 (DELTA 3), was a Phase 3, multicentre, uncontrolled, open-label study to evaluate the long-term safety and long-term efficacy of twice-daily applications of delgocitinib cream 20 mg/g as needed (based on the IGA score).

Patients who completed 1 of the 2 parent studies without prematurely discontinuing the study drug or receiving rescue treatment were eligible.

The study included a 1- to 4-week screening period, a 36-week treatment period (adding up to 52 weeks of consecutive treatment in total), and a 2-week safety follow-up period.

During the 36-week treatment period, the patients were treated "as needed" and could therefore be on and off treatment multiple times based on their IGA score:

- Patients with an IGA score of 0 or 1 at LTE baseline (study 1401 and 1402 responders) started off treatment in the LTE. After receiving an IGA score of at least 2 points, patients initiated (vehicle responders) or re-initiated (verum responders) treatment with delgocitinib 20mg/g. After receiving an IGA score of 0 or 1, patients stopped the treatment.
- Patients with an IGA score of at least 2 points at LTE baseline (study 1401 and 1402 non-responders) initiated (vehicle non-responders) or continued (verum non-responders) treatment with delgocitinib 20mg/g. After receiving an IGA score of 0 or 1, patients stopped the treatment. After receiving an IGA score of at least 2 points, patients re-initiated the treatment.

The primary objective was to evaluate the long-term safety of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g, and the corresponding primary endpoint was the "number of treatment-emergent AEs from baseline up to Week 38".
The secondary objective was to evaluate the long-term efficacy of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g, and the corresponding secondary endpoints were:

- IGA score at each scheduled visit from baseline up to Week 36
- Proportion of patients with an IGA score of 0 (clear) or 1 (almost clear) at each scheduled visit from baseline up to Week 36

- Hand eczema severity index (HECSI) score at each scheduled visit from baseline up to Week 36
- At least a 75% improvement in HECSI score from baseline (HECSI-75) at each scheduled visit from baseline up to Week 36
- At least a 90% improvement in HECSI score from baseline (HECSI-90) at each scheduled visit from baseline up to Week 36

The results for the primary endpoint are included in the “Safety” section (see below).

The efficacy results showed a similar response rate at Week 36 as at Week 0 (i.e. Weeks 52 and 16, respectively, from the start of the parent studies DELTA 1 and 2), which is suggestive of the maintenance of the treatment effect; however, no firm conclusions can be drawn about the long-term efficacy of delgocitinib until Week 52 due to the uncontrolled study design and a possibly variable natural course of the disease.
The detailed efficacy results are presented in the Swiss Information for healthcare professionals.

Study 1528 (DELTA Force)

Study 1528 (DELTA Force) was a Phase 3, multi-centre, randomised, assessor-blinded, active (alitretinoin)-controlled, parallel-group study in adult patients with moderate to severe CHE.

The study enrolled adult patients with severe CHE and a documented inadequate response to treatment with TCS, or for whom TCS were documented to be otherwise medically inadvisable.

Study 1528 (DELTA Force) had a 1- to 4-week long screening period.
Eligible patients were then randomised 1:1 to 1 of 2 treatment groups for treatment with either topical delgocitinib cream 20 mg/g twice daily for 16 consecutive weeks or oral alitretinoin 30 mg once daily (with an option to reduce to 10 mg during the study) for 12 consecutive weeks. In both groups, study treatment could be extended up to 24 weeks depending on IGA status or clinical benefit.
Randomisation was stratified by subtype of eczema and region. Patients were not blinded to the treatment, but the efficacy assessors were blinded to the treatment. Further, sponsor staff were also blinded.
Week 24 of the treatment period was followed by a 2-week follow-up period.

In study 1528 (DELTA Force), a statistically significant higher number of patients achieved the primary and the most important secondary efficacy endpoints in the delgocitinib cream treatment group compared to the alitretinoin oral capsule treatment group. The detailed results for the primary and secondary efficacy endpoints can be found in the Swiss Information for healthcare professionals.

6.4 Safety

Safety pools and exposure to study drug
The clinical safety assessment relied on the most relevant safety pools, i.e. the primary and long-term safety pools:
The primary safety pool encompassed the safety data from the pivotal studies 1401 and 1402 (DELTA 1 and 2), as well as the safety data from the delgocitinib 20 mg/g and the vehicle treatment groups of dose-finding study 1273, resulting in approximately 215 patient-years of observation.

The long-term safety pool with exposures up to > Week 52 in total encompassed the safety data from the pivotal studies 1401 and 1402 (DELTA 1 and DELTA 2) as well as from their LTE study 1403 (DELTA 3), resulting in approximately 500 patient-years of observation.

Results based on the primary safety pool

AEs
The most common AEs belonged to the system organ class Infections and Infestations.
Influenza (1.8 vs. 0.6%), upper respiratory tract infections (1.7 vs. 0.3%), and oral herpes (1.2% vs. 0.8%) occurred more often on delgocitinib versus vehicle.

Severe AEs
Severe AEs were rare in both treatment groups (delgocitinib 2.1% vs. 2.7% for vehicle).
The most common severe AEs on delgocitinib were gastroenteritis (2 cases, 0.3% vs. 0%), COVID-19 pneumonia (1 case, 0.1% vs. 0%), and 1 case of gallbladder adenocarcinoma.

Serious adverse events (SAEs)
0.6% of patients on delgocitinib reported serious infections (0% on vehicle).
The reported SAEs included single cases of COVID-19 pneumonia, peritonsillar abscess, bacterial keratitis, and tonsillitis.
Further, single-cases of epilepsy, migraine, and generalised tonic-clonic seizure were reported solely on delgocitinib.

Deaths
No deaths were reported during studies 1273, 1401 (DELTA 1), and 1402 (DELTA 2).

Results based on the long-term safety pool

Definition of exposure duration quartiles

Subjects exposed to delgocitinib cream 20 mg/g were grouped in cumulative delgocitinib exposure duration quartiles based on actual time on delgocitinib treatment: <25 weeks (Q1), 25 to <36 weeks (Q2), 36 to <49 weeks (Q3), and ≥49 weeks (Q4).

Adverse events (AEs)

No general pattern of increasing rates of AEs with increased delgocitinib exposure was seen, and the rates were generally lower compared to the vehicle group of the primary safety pool.

Events of gastroenteritis were reported at a higher rate in the longest exposure quartile (Q4). None of the events were serious, and the vast majority were mild to moderate. All events resolved within a maximum of 8 days without any impact on study conduct.

Hypertension occurred approximately 3 times more often (exposure-adjusted) in patients treated with delgocitinib versus vehicle cream. All of these patients already had elevated blood pressure prior to starting the study drug. However, such imbalances between treatment groups are usually eliminated by means of randomisation. Therefore, an uncertainty remains as to whether hypertension can be caused by Anzupgo (which would also imply systemic exposures) or not.

Safety focus areas

a) Infections: No pattern of increasing rates over time was seen, including serious or severe infections.

b) Cardiovascular (CV) events: Two CV AEs were reported in study 1403: 1 case of “death” and 1 fatal case of myocardial infarction in Q1. Both cases are also mentioned below under *g) Mortality*. No general safety concern can be derived from these single cases*.

c) Embolic and thrombotic events: Three embolic or thrombotic events were reported in patients with previous (in parent study) and/or current (in LTE study) delgocitinib treatment (1 case of thrombophlebitis, the above-mentioned fatal myocardial infarction, and 1 case of venous thrombosis)*.

d) Malignancies: Four malignancies were reported in 4 patients from delgocitinib treatment groups (gallbladder adenocarcinoma, oesophageal cancer metastatic, basal cell carcinoma (non-melanoma skin cancer), intraductal proliferative breast lesion). No definite conclusions on the risk for malignancies of Anzupgo can be drawn due to the limited total exposure (time)*.

e) Low blood cell counts: Low blood cell counts fluctuated but generally decreased over the observation time. High rates in Q3 were mainly driven by lymphopenia and decreased lymphocyte counts, with 3 events each. All events were non-serious, of mild or moderate severity, and did not lead to interruption or discontinuation of the study or study drug.

f) Lipid parameters: There was no increase in the rate of hypercholesterolaemia with long-term delgocitinib cream 20 mg/g treatment (primary pool: R=2.24, compared to the long-term safety pool: R=1.66).

g) Mortality: Three deaths were reported in study 1403, all involving patients who had received delgocitinib: 1 case of fatal metastatic oesophageal cancer, 1 case of death after a fall, and 1 fatal case of myocardial infarction. They were most likely not linked to the study drug. No general safety concern can be derived from these cases, which showed no pattern*.

* Due to the limited total exposure to Anzupgo in patients with CHE and due to the single or low number of observed cases of these AEs without a discernible pattern, no definite conclusions can be drawn regarding their relatedness or unrelatedness to Anzupgo. However, these types of AEs are covered by the Information for healthcare professionals, “Warnings and Precautions” section, where the SAEs are described as being observed with other systemically available JAK inhibitors in other patient populations.

6.5 Final clinical benefit-risk assessment

Two identical pivotal studies (1401 and 1402 or DELTA 1 and 2) with clinically relevant endpoints demonstrated a low to moderate beneficial effect after 16-week treatment with delgocitinib 20 mg/g cream in comparison to vehicle cream in adult patients with moderate and severe CHE, who had failed to respond to, or not been eligible for, treatment with topical corticosteroids. The primary analyses were supported by sensitivity and tipping-point analyses.
A subsequent common long-term extension study (1403 or DELTA 3) with “as needed” delgocitinib 20 mg/g cream indicated that the treatment effect is maintained up to 52 weeks. It remains unknown whether the achieved treatment effect will be maintained for a period longer than 52 weeks.
Patients who achieved IGA treatment success on delgocitinib after 16 weeks had a median time to loss of response “off-treatment” of 4 weeks, which is considered short, especially bearing in mind that re-achieving IGA treatment success would take a median of 8 weeks.

The active-controlled Phase 3 study 1528 (DELTA Force) demonstrated a clinically relevantly greater treatment benefit for delgocitinib 20 mg/g cream in comparison to oral alitretinoin and a more favourable safety profile.

Systemic delgocitinib concentrations are measurable in patients after topical application, and a relative bioavailability of approximately 0.6 % was evaluated. The measured concentrations are low and highly variable. Therefore, continuous systemic JAK inhibition is unlikely in the patient population if the cream is applied as intended. However, it cannot be excluded that pharmacologically relevant systemic exposures are reached temporarily. The cream amount used per application was found to be the predominant factor influencing the observed systemic concentration; thus, a limitation of the maximum drug amount used to 60 g cream per month is implemented.
For breastfeeding women, since a risk of cross-contamination to the child by normal care activities cannot be ruled out, a restriction for breastfeeding women is implemented.

Overall, the observed safety profile of treatment with delgocitinib 20 mg/g cream for up to 52 weeks is acceptable and considered manageable. However, it remains unknown whether this will also be maintained for longer periods of time, especially in regard to the known JAK inhibitor-linked safety concerns. As a safety measure, the SAEs that have been observed with *other systemically available* JAK inhibitors in *other* patient populations are described in the Information for healthcare professionals, “Warnings and Precautions” section.

Compared to alitretinoin, delgocitinib demonstrates a more favourable safety profile for up to 24 weeks of treatment. It remains unknown whether this remains true for a longer treatment period.

Based on the submitted data, the benefit-risk analysis for delgocitinib in the treatment of chronic hand eczema was considered positive. The indication was adjusted to better reflect the study population of the pivotal studies, specify further conditions for successful therapy in this indication, and to align with the wording of the indications of other medicinal products approved in Switzerland for the same indication.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Anzupgo was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Anzupgo®

Composition

Active substances

Delgocitinib.

Excipients

10 mg/g benzyl alcohol (E1519), 0,2 mg/g butylhydroxyanisole (E 320), 72 mg/g cetostearyl alcohol, citric acid monohydrate, sodium edetate, hydrochloric acid, liquid paraffin, macrogol 22 cetostearyl ether, purified water.

Pharmaceutical form and active substance quantity per unit

Cream, white to slightly brown.
1 g of Anzupgo® contains 20 mg of delgocitinib.

Indications/Uses

Anzupgo® is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom a treatment with potent to very potent topical corticosteroids is not recommended. Avoiding contact with the triggering noxa, skin protection and basic care are important components of the therapy.

Dosage/Administration

Usual dosage

A thin layer of Anzupgo® should be applied twice daily to the affected skin area of the hands and wrists until the skin is clear or almost clear.

In the event of recurrence of the signs and symptoms of CHE (flares), twice daily treatment of the affected areas may be re-initiated as needed.

No more than 1 tube of 60 g per month should be administered.

Special dosage instructions

Patients with hepatic disorders

Dose adjustment is not recommended due to the low systemic exposure of topically applied delgocitinib (see «Pharmacokinetics»).

Patients with renal disorders

No studies with Anzupgo® have been performed in patients with severe renal impairment. However, dose adjustment is not recommended due to the low systemic exposure of topically applied delgocitinib (see «Pharmacokinetics»).

Elderly patients

No dose adjustment is recommended for elderly patients (≥ 65 years).

Children and adolescents

Anzupgo® is not approved for use in the paediatric population. The safety and efficacy of Anzupgo® in children and adolescents under 18 years of age have not been established (see «Properties/Effects»). No data are available.

Delayed administration

If an application is missed, Anzupgo® should be applied as soon as possible. Thereafter, resume the application at the regular scheduled time.

Mode of administration

Anzupgo® is for topical use only.

A thin layer of Anzupgo® should be applied twice daily to clean and dry skin of the affected areas of the hands and wrists. Application of other topical products right before and after application of Anzupgo® should be avoided. Co-application with emollients within 2 hours before and after application of delgocitinib has not been studied.

If someone else applies the cream to the patient, they should be instructed to wash their hands after application.

Contact with healthy skin, eyes, mouth, genitals or other mucous membranes should be avoided. If contact occurs, rinse thoroughly with water.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in «Composition».

Warnings and precautions

During treatment with Anzupgo®, low systemic delgocitinib concentrations were observed in most patients and consequently a systemic pharmacologic effect is rather not expected. In some patients temporarily increased delgocitinib concentrations were observed, so that undesirable systemic pharmacologic effects, including the below listed class effects of oral JAK inhibitors for chronic inflammatory diseases cannot be excluded. Therefore, weigh the benefits and risks before initiating a treatment with Anzupgo®.

The following adverse effects have been observed with other systemically JAK inhibitors for chronic inflammatory diseases:

Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been occurred in patients receiving oral JAK inhibitors.

The use of Anzupgo® should be avoided in following patients with an active, severe infection, including localized infections:

- Patients with chronic or recurrent infections
- Patients with a history of severe or opportunistic infection
- Patients who have been exposed to tuberculosis
- Patients who have resided or travelled in areas with endemic tuberculosis or endemic mycoses; or
- Patients with underlying conditions that may predispose them to infection.

Closely monitor patients for signs and symptoms of infection during and after treatment with Anzupgo®.
Interrupt treatment with Anzupgo® if a patient develops a serious infection, an opportunistic infection, or sepsis.
Do not resume treatment with Anzupgo® until the infection is controlled.

Tuberculosis (TB)

Cases of active tuberculosis were reported in clinical trials of oral JAK inhibitors for the treatment of chronic inflammatory diseases. Consider evaluating patients for latent and active TB infections prior to administration of Anzugpo®. During Anzugpo® use, patients should be monitored for the development of signs and symptoms of TB.

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with JAK inhibitors. If a patient develops herpes zoster, a temporary interruption of Anzugpo® until the episode resolves should be considered.

The effects of JAK inhibitors used to treat inflammatory conditions on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials.

Hepatitis B viral load (HBV-DNA titer) increases, with or without accompanying elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infection taking an oral JAK inhibitor.Malignancies (excluding NMSC), Major Adverse Cardiovascular Events (MACE), Thromboembolic Events and All-cause Mortality

In a large, randomized, post-marketing safety study of an oral JAK inhibitor in rheumatoid arthritis (RA) patients from 50 years of age, who had at least one cardiovascular risk factor, the following adverse effects were more frequently observed in patients treated with oral JAK inhibitor compared to patients treated with TNF blockers:

- Malignancies (excluding NMSC), particularly lung cancer and lymphomas.
- MACE, defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke. Patients should be informed about the symptoms of serious cardiovascular events and the measures to be taken if they occur. Discontinue Anzugpo® in patients who have experienced a myocardial infarction or stroke.
- Thromboembolic events, including deep vein thrombosis and pulmonary embolism as well as arterial thrombosis. Many of those adverse effects were serious and some resulted in death. Avoid Anzugpo® in patients with an increased risk of thrombosis. If symptoms of thrombosis occur, discontinue Anzugpo® and evaluate and treat patients appropriately.
- All-cause mortality.

Current and past smokers had an additional increased risk of these adverse effects.

Non-melanoma Skin Cancer (NMSC)

NMSC (basal cell carcinoma) were observed during treatment with Anzupgo®. With another topical JAK-inhibitor squamous cell carcinoma were also occurred. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad spectrum sunscreens.

Thrombocytopenia, Anaemia and Neutropenia

Thrombocytopenia, anaemia and neutropenia have been reported in clinical trials with JAK inhibitors. Perform blood count monitoring as clinically indicated. If signs and symptoms respectively of clinically significant thrombocytopenia, anaemia and neutropenia occur, discontinue the treatment of Anzugpo®.

Accidental exposure

As a precautionary measure, direct skin contact with other persons (especially newborns and infants, see «Lactation») right after applying the cream to the hands and/or wrists should be avoided. In the event of accidental transfer of cream, the cream can be wiped off. As risk for local and systemic effects due to unintentional transmission of Anzupgo® to other persons (especially newborns or infants) cannot be excluded (see also «Lactation»).

If someone else applies Anzupgo® to the patient, they should be instructed to wash their hands after application.

Contact with healthy skin, eyes, mouth, or other mucous membranes shall be avoided. If contact occurs, rinse thoroughly with water.

This medicinal product contains 10 mg/g benzyl alcohol per g cream. Benzyl alcohol may cause allergic reactions and mild local irritations. This medicinal product also contains 0,2 mg/g butylhydroxyanisole and 72 mg/g cetostearyl alcohol which may cause local skin irritations (e.g., contact dermatitis). Butylhydroxyanisole may also cause irritations to the eyes and mucous membranes.

Interactions

The metabolism of delgocitinib is low, therefore there is a low risk of potential interaction with systemic medicinal products (see «Pharmacokinetics»).

Based on *in vitro* data, delgocitinib does not inhibit or induce either cytochrome P450 enzymes or inhibit transporter systems such as organic anion transporters (OAT), organic anion transporting proteins (OATP), organic cation transporters (OCT), breast cancer resistance protein (BCRP), or multi-antimicrobial extrusion protein (MATE) at clinically relevant concentrations.

No clinical interaction studies have been performed. Anzupgo® has not been evaluated in combination with other topical medicinal products and co-application on the same skin area is not recommended.

Pregnancy, lactation

Pregnancy

There is limited data from the use of delgocitinib in pregnant women.

Studies, in which delgocitinib was orally administered in animals, have shown reproductive toxicity at exposures, which were considered sufficiently in excess of the human exposure following topical application (see «Preclinical data»).

As a precautionary measure, Anzupgo® should not be used during pregnancy.

Lactation

It is unknown whether delgocitinib is excreted in human milk.

After oral administration, delgocitinib was present in the milk of lactating rats (see «Preclinical data»).

A risk to the suckling child cannot be excluded. As a precautionary measure, Anzupgo® should not be used during breast-feeding (see “Warnings and Precautions” - Accidental exposure)
When Anzupgo® is used during breast-feeding, care should be taken to avoid direct contact with the nipple or surrounding area after applying the cream to the hands and/or wrists.

Fertility

No human data on the effect of delgocitinib on fertility are available.

Based on findings in female rats, oral administration of delgocitinib resulted in reduced fertility at exposures considered sufficiently in excess of the human exposure (see «Preclinical data»).

Animal studies did not indicate effects with respect to fertility in male animals.

Effects on ability to drive and use machines

Anzupgo® has no or negligible influence on the ability to drive and to use machines.

Undesirable effects

Summary of the safety profile

The most common adverse reactions were application site reactions (1,0%).
The safety data described below are based on a pool of three vehicle-controlled clinical studies in 1062 patients with chronic hand eczema, of which 691 were treated with delgocitinib cream (20 mg/g) twice daily for up to 16 weeks. In the open-label long-term extension study (see «Properties/Effects»), safety up to 52 weeks was observed.

List of adverse reactions

The following adverse reactions were observed in clinical trials and are presented according to MedDRA system organ classes and the below listed frequency categories:
«very common» (≥1/10)
«common» (≥1/100, <1/10),
«uncommon» (≥1/1’000, <1/100)
«rare» (≥1/10’000, <1/1’000)
«very rare» (<1/10’000)

General disorders and administration site conditions
Common: Application site reactions

Description of specific adverse reactions and additional information

Application site reactions

In the pool of three vehicle-controlled clinical studies through 16 weeks, application site reactions (including application site pain, application site paraesthesia, application site pruritus, and application site erythema) were reported in 1,0% of patients treated with delgocitinib cream compared with 2,5% of patients treated with vehicle cream. The majority of these reactions were mild in severity. No serious or severe events were reported. Of the application site reactions observed in patients receiving delgocitinib cream treatment, over 75% occurred within the first week of treatment, none resulted in treatment interruption, and the median time to resolution was 3 days.
The event rate of application site reactions in the long-term extension study (0,56 events per 100 patient years of observation) was lower than in the 16-week vehicle-controlled clinical studies (4,11 events per 100 patient years of observation).

Dermal Safety Studies

The results of clinical studies in healthy subjects demonstrated that delgocitinib cream did not cause phototoxic or photoallergic skin reactions.

Cardiac electrophysiology

In a concentration QT analysis in healthy subjects, there was no indication of a QTc prolonging effect following orally administered delgocitinib at single doses up to 12 mg (approximately 200 times the human exposure following topical application, based on C_{max}). Therefore, Anzupgo® is not expected to affect cardiac repolarisation under conditions of clinical use.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Due to the low systemic absorption of delgocitinib risks for systemic undesirable effects cannot be completely excluded following an overdose of topical application of Anzupgo®. If too much cream has been applied, the excess should be wiped off (see also «Art of administration», «Warnings and Precautions» – *Accidental exposure*).

Properties/Effects

ATC code

D11AH11

Mechanism of action

Delgocitinib is a pan Janus kinase (JAK) inhibitor that targets the activity of all four members of the JAK family of enzymes consisting of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) in a concentration dependent manner. Janus kinases are intracellular enzymes associated with cytokine receptor chains that transmit signals from cytokines to regulate a broad range of physiological and pathological processes, including inflammatory responses. Within the signalling pathway, JAKs are activated upon cytokine-receptor interaction and thereafter phosphorylate and activate signal transducers and activators of transcription (STATs). Activated STATs, in turn, activate the expression of cytokine-responsive genes to induce specific biological responses in target cells. Inhibition of JAK activity with delgocitinib prevents the phosphorylation and activation of STATs.

In human cellular studies, inhibition of the JAK-STAT pathway by delgocitinib attenuates the signalling of several pro-inflammatory cytokines (including interleukin (IL)-2, IL-4, IL-6, IL-13, IL-21, IL-23, Granulocyte-Macrophage-Colony-Stimulating Factor (GM-CSF), and Interferon (IFN)-α) downregulating the immune and inflammatory responses in cells of relevance to CHE pathology.

Pharmacodynamics

In patients with chronic hand eczema (CHE), treatment with topically applied delgocitinib resulted in reduced levels of pro-inflammatory markers of CHE such as S100 calcium binding protein A9/12 (S100A9/12), and serpin family B member 3 (SERPINB3).

Treatment with topically applied delgocitinib also resulted in the increased expression of genes involved in skin barrier function (e.g., filaggrin, loricrin, and claudins) in lesional skin.

Skin colonisation with *Staphylococcus aureus* was greatly reduced compared to vehicle.

Clinical efficacy

The safety and efficacy of delgocitinib cream were evaluated in two pivotal randomised, double-blind, vehicle-controlled studies of the same design (DELTA 1 and DELTA 2). The studies included 960 patients 18 years of age and older with moderate to severe CHE as defined by an Investigator's Global Assessment for chronic hand eczema (IGA-CHE) score of 3 or 4 (moderate or severe) (see Table 1) and required a Hand Eczema Symptom Diary (HESD) itch score of ≥ 4 points at baseline. Eligible patients had a previous inadequate response to potent to very potent topical corticosteroids or were those in which potent to very potent topical corticosteroids are not advisable.

Table 1: Investigator's Global Assessment for chronic hand eczema (IGA-CHE)

IGA-CHE severity	IGA-CHE score	Sign and intensity
Clear	0	No signs of erythema, scaling, hyperkeratosis/lichenification, vesiculation, oedema or fissures
Almost clear	1	Bare perceptible erythema No signs of scaling, hyperkeratosis/lichenification, vesiculation, oedema or fissures
Mild	2	At least one: • Slight but definite erythema (pink) • Slight but definite scaling (mostly fine scales) • Slight but definite hyperkeratosis/lichenification and at least one: • Scattered vesicles, without erosion • Barely palpable oedema • Superficial fissures
Moderate	3	At least one: • Clearly perceptible erythema (dull red) • Clearly perceptible scaling (coarse scales) • Clearly perceptible hyperkeratosis/lichenification and at least one: • Clustered vesicles, without visible erosions • Definite oedema • Definite fissures
Severe	4	At least one: • Marked erythema (deep or bright red) • Marked and thick scaling • Marked hyperkeratosis/lichenification and at least one: • High density of vesicles with erosions • Marked oedema • One or more deep fissures

In DELTA 1 and DELTA 2, patients applied either delgocitinib cream (20 mg/g) or vehicle cream twice daily to affected areas on the hands and wrists for 16 weeks. All patients who completed the two pivotal studies were eligible to enrol into the long-term extension study DELTA 3.

Endpoints

In DELTA 1 and DELTA 2, the primary endpoint was achieving IGA-CHE treatment success (IGA-CHE TS), defined as an IGA-CHE score of 0 (clear) or 1 (almost clear: barely perceptible erythema only) with at least a 2-step improvement from baseline to Week 16. The IGA-CHE instrument rates the severity of the subject's global disease and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (see Table 1).

Additional efficacy outcomes included the Hand Eczema Severity Index (HECSI) and the HESD at various timepoints. The HECSI rates the severity of six clinical signs (erythema, infiltration/papulation,

vesicles, fissures, scaling, and oedema) and the extent of the lesions on each of the five hand regions (fingertips, fingers, palm of hands, back of hands, and wrists). The HESD is a daily 6-item patient reported outcome (PRO) instrument designed to assess the worst severity of signs and symptoms of CHE (itch, pain, cracking, redness, dryness, and flaking) using an 11-point numeric rating scale.

Baseline characteristics

Across all treatment groups in DELTA 1 and DELTA 2, the mean age was 44,1 years, 7,6% of patients were 65 years of age or older, 64,4% were female, 90,4% were White, 3,5% were Asian, and 0,7% were Black. The frequency of CHE by main subtype was 35.9% atopic hand eczema, 21.5% hyperkeratotic eczema, 19.6% irritant contact dermatitis, 13.9% allergic contact dermatitis, 9.1% vesicular hand eczema (pompholyx), and 0.1% contact urticaria/protein contact dermatitis. In DELTA 1 and DELTA 2, 28,4% of patients had a baseline IGA-CHE score of 4 (severe CHE). The mean baseline Dermatology Life Quality Index (DLQI) score was 12,5, HECSI score was 71,6, and HESD score was 7,1. The mean HESD itch and pain scores were 7,1 and 6,7, respectively.

Clinical response

DELTA 1 and DELTA 2

In DELTA 1 and DELTA 2, a significantly greater proportion of patients randomised to delgocitinib cream achieved the primary endpoint of IGA-CHE TS compared to vehicle at Week 16. The results for the primary and selected other multiplicity-controlled secondary endpoints are presented in Table 2. Figure 1 shows the proportion of patients who achieved HECSI-75, HESD itch ≥ 4-point improvement, and HESD pain ≥ 4-point improvement over time in DELTA 1 and DELTA 2.

Table 2: Efficacy results of delgocitinib at Week 16 in DELTA 1 and DELTA 2

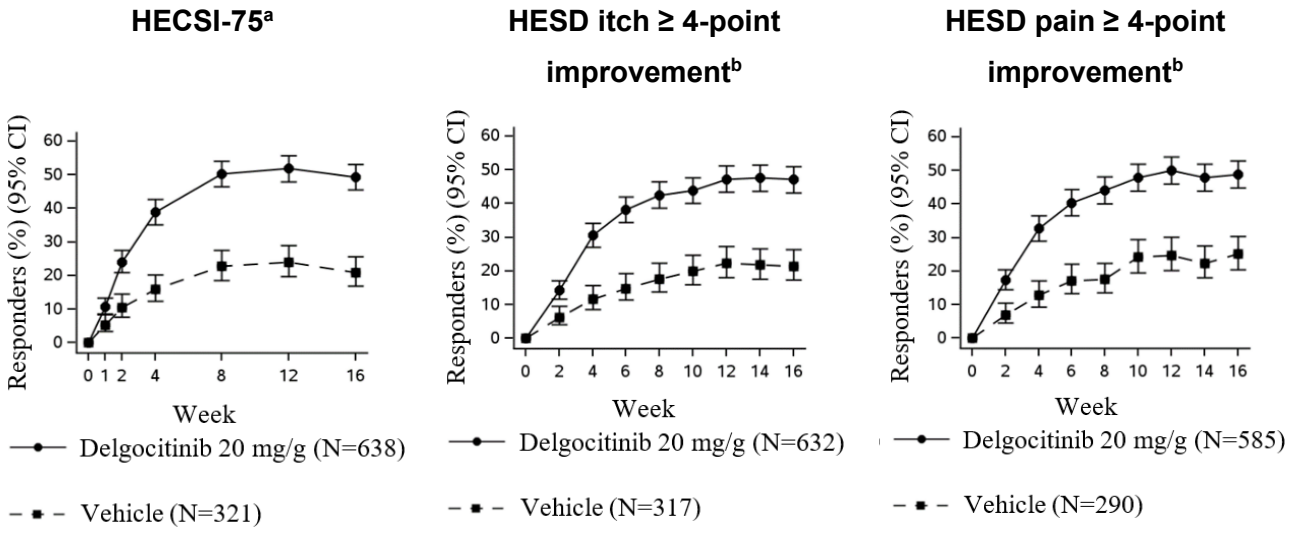
	DELTA 1		**DELTA 2**	
	Delgocitinib (N=325)	**Vehicle (N=162)**	**Delgocitinib (N=313)**	**Vehicle (N=159)**
IGA-CHE TS, % responders[a, b]	19,7[#]	9,9	29,1[§]	6,9
HECSI-90, % responders[a, c]	29,5[§]	12,3	31,0[§]	8,8
HECSI-75, % responders[a, d, e]	49,2[§]	23,5	49,5[§]	18,2
HECSI, LS mean % change from baseline (± SE)[f]	-56,5[§] (± 3,4)	-21,2 (± 4,8)	-58,9[§] (± 3,2)	-13,4 (± 4,5)
HESD itch score, LS mean change from baseline (± SE)[f]	-3,6[§] (± 0,2)	-1,9 (± 0,2)	-3,4[§] (± 0,2)	-1,4 (± 0,2)
HESD pain score, LS mean change from baseline (± SE)[f]	-3,4[§] (± 0,2)	-1,8 (± 0,2)	-3,3[§] (± 0,2)	-1,3 (± 0,2)
HESD score, LS mean change from baseline (± SE)[f]	-3,4[§] (± 0,1)	-1,7 (± 0,2)	-3,2[§] (± 0,1)	-1,4 (± 0,2)
HESD itch ≥ 4-point improvement, % responders[a, g, h]	47,1[§] (152/323)	23,0 (37/161)	47,2[§] (146/309)	19,9 (31/156)
HESD pain ≥ 4-point improvement, % responders[a, b, g]	49,1[§] (143/291)	27,5 (41/149)	48,6[§] (143/294)	22,7 (32/141)
HESD ≥ 4-point improvement, % responders[a, b, g]	47,2[§] (146/309)	24,4 (38/156)	44,5[§] (137/308)	20,9 (32/153)

[#]p<0,01, [§]p<0,001
All p-values were statistically significant versus vehicle with adjustment for multiplicity
Abbreviations: LS=least squares; N=number of patients in the full analysis set (all patients randomised and dosed); SE = standard error

a. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-response.
b. Statistically significant versus vehicle with adjustment for multiplicity at Week 4 and 8 in DELTA 1 and DELTA 2
c. HECSI-90 responders were patients with ≥ 90% improvement in HECSI from baseline.
d. HECSI-75 responders were patients with ≥ 75% improvement in HECSI from baseline.
e. Statistically significant versus vehicle with adjustment for multiplicity at Week 8 in DELTA 1 and DELTA 2
f. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-response by using worst observation carried forward.
g. Based on the number of patients whose baseline value was ≥ 4 (scale from 0-10).
h. Statistically significant versus vehicle with adjustment for multiplicity at Week 2, 4, and 8 in DELTA 1 and DELTA 2

Greater improvements measured by the mean change in HESD itch and pain scores compared to vehicle, were observed as early as 1 day and 3 days after starting delgocitinib treatment, respectively. By Week 2, greater improvements versus vehicle were observed for all the HESD items (itch, pain, cracking, redness, dryness, and flaking).

Figure 1: Proportion of patients who achieved HECSI-75, HESD itch ≥ 4-point improvement, and HESD pain ≥ 4-point improvement over time pooled data from DELTA 1 and DELTA 2



CI = Confidence Interval
a. HECSI-75 responders were patients with ≥ 75% improvement in HECSI from baseline.
b. Based on the number of patients whose baseline value was ≥ 4 (scale from 0-10).

Across DELTA 1 and DELTA 2, treatment effects in subgroups (weight, age, gender, disease severity, duration of CHE, and previous treatment) were consistent with the results in the overall study population.

The point estimates of treatment effect for the primary and key secondary endpoints at Week 16 were consistently in favor of delgocitinib for all CHE subtypes, however for hyperkeratotic hand eczema the estimated treatment difference for IGA-CHE TS was 2.1%, 95% CI (-6.8:11.0). For all CHE subtypes, there was a statistically significantly greater improvement in HESD itch and pain (≥ 4-point improvement) at Week 16 compared to cream vehicle.

Additional quality of life/patient-reported outcomes

In both DELTA 1 and DELTA 2, patients treated with delgocitinib cream showed a significant improvement from baseline to Week 16 compared to vehicle in the Hand Eczema Impact Scale (HEIS) (proximal daily activity limitations, embarrassment, frustration, sleep, work, and physical functioning [ability to hold or grip objects]) (see Table 3).

Across DELTA 1 and DELTA 2, significantly greater improvements in health-related quality of life, as measured by the DLQI were observed in delgocitinib patients compared to vehicle at Week 16 (see Table 3). Of the four domains of the Work Productivity and Activity Impairment: Chronic Hand Eczema instrument (absenteeism, presenteeism, work productivity loss, and activity impairment), patients receiving delgocitinib cream demonstrated greater improvements in all domains except for absenteeism compared to vehicle at Week 16.

Table 3: Quality of life/patient reported outcomes results of delgocitinib at Week 16 in DELTA 1 and DELTA 2

	DELTA 1		**DELTA 2**	
	Delgocitinib (N=325)	**Vehicle (N=162)**	**Delgocitinib (N=313)**	**Vehicle (N=159)**
DLQI, LS mean change from baseline (± SE)[a]	-7,6[§] (± 0,3)	-3,9 (± 0,4)	-7,0[§] (± 0,3)	-3,1 (± 0,5)
HEIS, LS mean change from baseline (± SE)[a]	-1,46[§] (± 0,05)	-0,82 (± 0,08)	-1,45[§] (± 0,06)	-0,64 (± 0,08)
HEIS PDAL, LS mean change from baseline (± SE)[a, b]	-1,46[§] (± 0,06)	-0,86 (± 0,08)	-1,48[§] (± 0,06)	-0,66 (± 0,08)
DLQI ≥ 4-point improvement, % responders[c, d]	74,4[§] (227/305)	50,0 (74/148)	72,2[§] (216/299)	45,8 (70/153)

[§]p<0,001
All p-values were statistically significant versus vehicle with adjustment for multiplicity
Abbreviations: LS=least squares; N=number of patients in the full analysis set (all patients randomised and dosed); PDAL=proximal daily activity limitations; SE=standard error

a. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-response by using worst observation carried forward.
b. HEIS PDAL assesses the patient's ability to use soaps/cleaning products, to do housework, and to wash themselves.
c. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-respondse.
d. Based on the number of patients whose baseline value was ≥ 4.

Extension study (DELTA 3)

Patients who completed either DELTA 1 or DELTA 2 were eligible to enrol in a 36-week open-label extension study (DELTA 3). In DELTA 3, the long-term safety and efficacy of as needed delgocitinib treatment was evaluated in 801 patients. Patients started application of delgocitinib cream twice daily to affected areas whenever the IGA-CHE score was ≥ 2 (mild or worse) and stopped treatment when an IGA-CHE score of 0 or 1 (clear or almost clear) was achieved. Patients entering DELTA 3 with an IGA-CHE score of 0 or 1 remained off treatment until loss of response (IGA-CHE score ≥ 2).

The proportions of patients achieving IGA-CHE 0 or 1, HECSI-75, HECSI-90, HESD itch ≥ 4-point improvement, and HESD pain ≥ 4-point improvement after the initial 16-week treatment period of

delgocitinib cream were maintained through Week 52 with as-needed treatment. Among the 560 patients randomised to delgocitinib cream treatment in the pivotal studies (DELTA 1 and DELTA 2) and enrolled in DELTA 3, the mean number of treatment periods was 1,5 (range 0 to 6), the mean treatment period duration was 123 days, and the mean cumulative number of days in response (days with an IGA-CHE score of 0 or 1 within the 36-week treatment period) was 46. The mean cumulative number of days in response was 111 among those patients who achieved IGA-CHE TS at Week 16 in the pivotal studies.

Of the patients randomised to delgocitinib cream in the pivotal studies who achieved IGA-CHE TS at Week 16, the median duration of response while off treatment was 4 weeks with 28% maintaining response for at least 8 weeks. The median time to regain an IGA-CHE score of 0 or 1 following re-initiation of treatment was 8 weeks. Among patients who did not achieve an IGA-CHE TS at Week 16 of delgocitinib treatment in the pivotal studies, 48,1% achieved IGA-CHE 0 or 1 with continued delgocitinib treatment in DELTA 3.

Phase 3 direct comparative study versus alitretinoin (DELTA Force)

The efficacy and safety of delgocitinib 20 mg/g cream twice-daily were evaluated in a randomized, assessor-blinded study compared with alitretinoin 30 mg capsules (with an option to reduce to 10 mg during trial conduct) once-daily in adult patients with severe CHE. The treatment duration was up to 24 weeks.

Statistically significant greater improvement for the primary endpoint, change in HECSI score from baseline to Week 12, was achieved for delgocitinib cream compared to alitretinoin. Statistically significant greater improvements were also achieved for delgocitinib for the key secondary endpoints, including HESD itch and HESD pain. The results for the primary and selected multiplicity-controlled secondary endpoints are presented in Table 4.

Table 4: Efficacy results at Week 12 from DELTA Force – delgocitinib versus alitretinoin

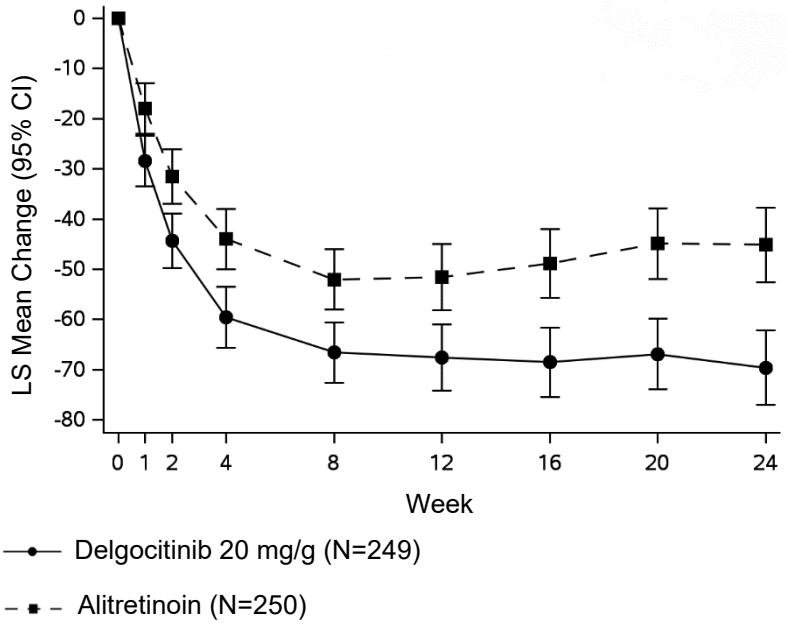
	DELTA Force	
	Delgocitinib (N=250)	**Alitretinoin (N=253)**
HECSI, LS mean change from baseline (± SE)[a]	-67.6[§] (±3,37)	-51,5 (±3,36)
HECSI-90, % responders[b]	38,6[#]	26,0
IGA-CHE TS, % responders[b]	27,2[#]	16,6
HESD itch score, LS mean change from baseline (± SE)[a]	-3,0[#] (± 0,22)	-2,4 (± 0,21)
HESD pain score, LS mean change from baseline (± SE)[a]	-2,9* (± 0,23)	-2,3 (± 0,23)

*p=0.018, [#]p<0,01, [§]p<0,001
All p-values were statistically significant versus alitretinoin with adjustment for multiplicity.
Abbreviations: LS=least squares; N=number of patients in the full analysis set; SE = standard error

a. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-response by using worst observation carried forward.
b. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-response

Greater improvements for delgocitinib cream measured by the mean change in HECSI score compared to alitretinoin capsules, were observed as early as Week 1 and continued to improve through to Week 24. Change in HECSI scores from baseline to Week 24 for delgocitinib and alitretinoin are presented in Figure 2.

Figure 2: LS mean change from baseline in HECSI score over time in DELTA Force



Abbreviations: CI=confidence interval; LS=least squares

Pharmacokinetics

Absorption

The pharmacokinetics of delgocitinib cream (20mg/g) were evaluated in a study involving 15 adult patients 22 to 69 years of age with moderate to severe CHE. Patients applied delgocitinib to the affected areas of the hands and wrists twice a day for 8 days.

The geometric mean ± SD maximum plasma concentration (C_{max}) and area under the concentration-curve from time 0 to 12 hours (AUC_{0-12}) on Day 8 was 0,46 ng/mL ± 0,28 and 3,7 ng*h/mL ± 1,88, respectively. No accumulation was observed. The systemic exposure (AUC and C_{max}) between Day 1 and Day 8 were similar.

Following twice daily application of delgocitinib in DELTA 2, the geometric mean plasma concentration (CV%) observed 2-6 hours after application at Day 113 was 48 % lower than that at Day 8 (0,11 ng/mL (460%) and 0,21 ng/mL (218%), respectively) with an observed high variability.

The mean relative bioavailability of delgocitinib following topical application of Anzupgo® is approximately 0,6% compared to oral administration of delgocitinib tablets.

Distribution

Plasma protein binding of delgocitinib is 22 to 29%.

Metabolism

As delgocitinib does not undergo extensive metabolism, the main plasma component is unchanged delgocitinib. Following oral administration, four metabolites (formed via oxidation and glucuronide conjugation) were detected at <2% of the average unchanged delgocitinib plasma concentrations. The limited metabolism of delgocitinib occurs primarily though CYP3A4/5 and to a lesser extent by CYP2C9, CYP2C19, and CYP2D6.

Elimination

Delgocitinib is primarily eliminated by renal excretion as approximately 75% of the total dose after oral administration was found unchanged in the urine.

Following repeated topical application, the average half-life of delgocitinib was estimated to be 20,3 hours. The observed half-life after topical administration is longer than observed after oral administration due to slow absorption following topical application.

Kinetics in specific patient groups

Hepatic impairment

No formal studies of delgocitinib cream in patients with hepatic impairment have been conducted.

Due to the low systemic exposure of topically applied delgocitinib and limited metabolism of delgocitinib, changes in hepatic function are unlikely to have any effects on the elimination of delgocitinib. Therefore, no dose adjustments are needed in patients with hepatic impairment (see «Dosage/Administration»).

Renal impairment

Pharmacokinetic parameters of delgocitinib were analysed in 96 patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min/1,73 m^2) in DELTA 2. The geometric mean plasma concentrations measured at Week 1 were 0.18 ng/ml (n=201), 0.29 ng/ml (n=80), and 0.41 ng/ml (n=6) in patients with no, mild, and moderate renal impairment, respectively. Due to the low systemic exposure of topically applied delgocitinib, changes in plasma concentration are unlikely to be of clinical importance in renal impairment. Therefore, no dose adjustments are needed in patients with renal impairment (see «Dosage/Administration»).

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, phototoxicity, local tolerability, skin sensitization, and juvenile toxicity.

Effects in repeat dose toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure following topical application.

Carcinogenicity

In a 2-year dermal carcinogenicity study in mice, no local or systemic neoplastic findings were observed at strengths up to 50 mg/g delgocitinib ointment (systemic exposures up to approximately 600 times the human exposure after topical application based on AUC).

Findings from a 2-year oral carcinogenicity study in rats included pancreatic acinar adenomas and lipoma of the skin and subcutaneous tissue (males only), thymoma (females only), and Leydig cell tumour at exposures approximately 160, 580, and 1800 times the human exposure after topical application, respectively. The clinical relevance of tumour findings in rats is low given the tumour types in a single species and single sex, the exposures at which the tumours occurred, and the negative findings in the 2-year dermal carcinogenicity study in mice.

Fertility and early embryonic development

Orally administered delgocitinib did not affect the fertility at any dose level evaluated in male rats (exposures approximately 1700 times the human exposure after topical application). In female rats, orally administered delgocitinib resulted in effects on female fertility (lower fertility index, fewer corpora lutea, and fewer implantations) at exposures approximately 5800 times the human exposure after topical application. Post-implantation losses and a decrease in the number of live embryos were observed at exposures approximately 432 and 1000 times the human exposure, respectively.

Embryo-foetal development

Orally administered delgocitinib did not result in harmful effects to the foetus in rats or rabbits at exposures approximately 120 and 194 times the human exposure after topical application, respectively.

In rats, decreases in foetal weight and skeletal changes (variations) were observed at exposures 512 times the human exposure after topical application and an increase in post-implantation loss, delayed fetal growth and delayed ossification were observed at exposures approximately 1400 times the human exposure after topical application. In rabbits, an increase in post-implantation loss, a reduced number of live foetuses, and a tendency toward a decrease in foetal weights were observed at exposures approximately 992 times the human exposure after topical application.

Pre-and postnatal development

Orally administered delgocitinib in rats resulted in decreased foetal viability, extended gestation period, extended duration of birth process, and reduced pup weights during the early postnatal period at exposures approximately > 1 400 times the human exposure after topical application. There was no

effect on behavioral and learning assessments, sexual maturation, or reproductive performance of the offspring at any dose studied.

Following oral administration to lactating rats, delgocitinib was secreted in milk at amounts approximately 3-fold those in blood plasma (based on the AUC).

Other information

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Shelf life after opening

Shelf life after opening is 12 months.

Special precautions for storage

Do not store above 30°C. Do not freeze.

Keep out of the reach of children.

Authorisation number

69330 (Swissmedic)

Packs

Tube with 60 g [B]

Marketing authorisation holder

LEO Pharmaceutical Products Sarath Ltd., Kloten
Domicile: Zurich

Date of revision of the text

June 2024